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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,091	05/06/2005	Juha-Matti Savola	TUR-168	2654

32954 7590 02/25/2010

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
02/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,091	SAVOLA ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/30/09 has been entered.

2. Applicant's arguments filed 12/30/09 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 23 and 25-33 are pending in this office action.

5. The information disclosure statement (IDS) submitted on 12/30/10 is acknowledged and has been reviewed.

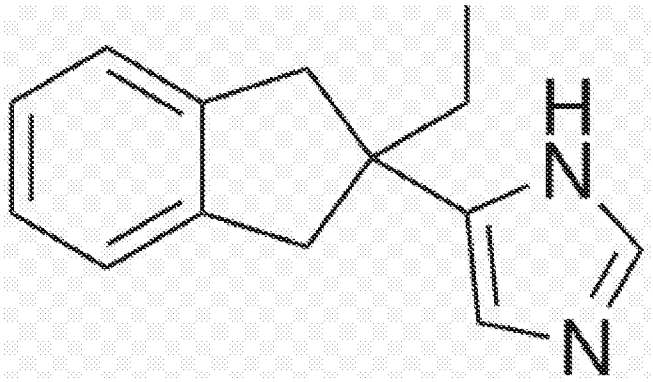
6. Claims 23, 25-29 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huupponen (1995) in view of Karjalainen et al., (US 5,498,623) for the reasons made of record in Paper No. 20090911 and as follows.

Applicant argues that the (i) "the problem of QTc prolongation (encountered when fipamezole is orally administered) is avoided when fipamezole is oromucosally administered. See Example 8 of the application and the Declaration Pursuant to 37 C.F.R. § 1.132 filed February 17, 2009".

(ii) Applicant further states that "[t]he applicants concede the combination of Huupponen et al. and Karjalainen et al. raises a prima facie case of obviousness against the claimed method. However, the claimed method produces an unexpected result (the absence of QTc prolongation) which cannot be predicted from the cited references and which overcomes the prima facie case". Applicant also argues further that both Huupponen et al. and Karjalainen et al. fail to disclose anything regarding QTc prolongation.

(iii) It is also argued that "Karjalainen et al. fails to expressly or inherently disclose oromucosal administration of fipamezole. Second, an obviousness rejection cannot be based on what is unknown. The applicants' initial discovery was fipamezole's inherent property to prolong the QTc interval when orally administered. Their subsequent discovery was fipamezole's inherent property not to prolong the QTc interval when oromucosally administered. Neither inherent property of fipamezole was previously known to those of ordinary skill in the art".

In response with regards to item (i) above, the claims are directed to a method of administering a formulation comprising an active ingredient of formula I, comprising oromucosal administration. Huupponen teaches administering atepamezole (i.e.,



) that has the same core, same class and functionally and structurally similar to the claimed compound fimpamezole wherein R1 and R2 are different substituents (i.e., hydrogen's in Huupponen versus halogen or hydroxy in the claimed invention). It should be noted that in regards to item (iii), "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990), "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established".

Further Huupponen teach that the above compound is administered oral mucosally (via spraying into the buccal cavity) and conducted assessment on the various pharmacokinetic parameters of the plasma resulted in no change in the plasma

concentration after oral administration. Huupponen confirms that no change in blood pressure was observed was seen with oral or buccal administration of the drug further teaches that the above drug is absorbed from the buccal mucosa to circulation with a bioavailability of 33%. Since QTc is associated with heart rate and the rate of the heart is unchanged, it is therefore reasonable that there is no prolongation of QTc was evident (see entire document). Secondly, the claims fail to recite a particular dosage amount, which is relevant in calculating a QTc value. There should be a correlation of amount administered with the QTc value. In the Affidavit, Appendix II, the data showed a dosage amount which is lacking in the claims.

Nonetheless, in regards to item (iii) "Applicant agrees with the Examiner that the combination of Huupponen et al. and Karjalainen et al. raises a prima facie case of obviousness against the claimed method". See item (i) above.

Additionally, with regards to item (iii) Examiner reiterates that this rejection is a rejection under 35 USC 103 and not a rejection under 35 USC102. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *See In re Keller,* 642 F 2d 413, 208 USPQ 871 (CCPA 1981)*; In re Merck &Co.,* 800 F.2d 1091, 231 USPQ (Fed. Cir. 1986).

Huupponen teaches atepamezole (i.e., see above structure) that has the same core, same class and functionally and structurally similar to the claimed compound fimpamezole. Atepamezole is a homolog of fipamezole and shares the same characteristics with fimpamezole. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious. In re Hass, 60 USPQ 544

(CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950). Also recognized classes of chemical compounds mean that there is an expectation in the art that members of the same class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other with the expectation that the same intended result would be achieved.

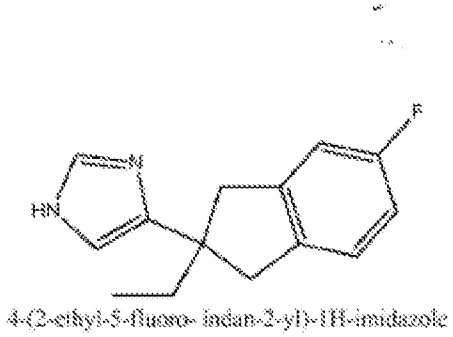
The teachings of Karjalainen encompass compounds of Huupponen, therefore one of ordinary skill in the art would be motivated to substitute Huupponen's compound with Karjalainen's compound and expect the same result. Therefore Applicant's argument that "one of ordinary skill in the art, aware that oral administration of fipamezole causes a dose-dependent prolongation of the QTc interval, would expect an equivalent or longer QTc prolongation if fipamezole was oromucosally administered" is found not persuasive because as clearly stated QTc is dose dependent. Moreover, the therapeutic activity that is relied upon by Applicant is a functional characteristic that is inherently or intrinsically present upon the administration of the drug in a certain dosage amount. The argument that the cited prior art fails to disclose or suggest that oromucosal administration of fipamezole will avoid QTc prolongation is found not persuasive because Huupponen specifically teach that in their study plasma, and heart rate were practically unchanged. Therefore if the plasma concentration is unchanged, there will be no "QTc prolongation", which further is not recited within the claims.

Applicant's arguments have been fully considered but they are not persuasive as discussed above and already made of record.

In Summary:

Huupponen teaches an α_2 adrenergic receptor antagonist (a species of the generic formula I in its acid salt) that is administered in the form of a spray oromucosally (see page 506, abstract; and Introduction as required by instant claim 23 in part, dissolved in ethanol and water (i.e., solvent; as required by instant claims 26- 27 in the form of spray as required by instant claims 31 and 32.

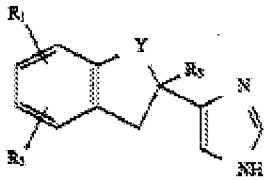
However Huupponen fails to teach the exact compound



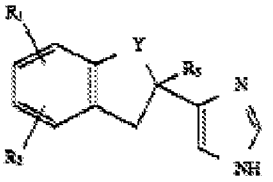
4-(2-ethyl-5-fluoro- indan-2-yl)-1H-imidazole

as required by instant claims 23 and 35 in part, and also fails to teach the formulation consists of a preservative (i.e., methyl parahydroxybenzoate) and the flavoring agent aspartame and black currant as in claims 29-30 and 33, and also the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29).

Karjalainen et al. teach the claimed compound as in current claim

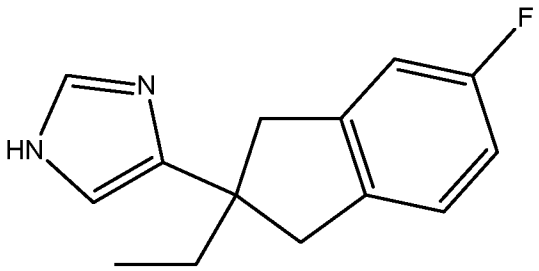


23 which is identical to the claimed compound of the claimed

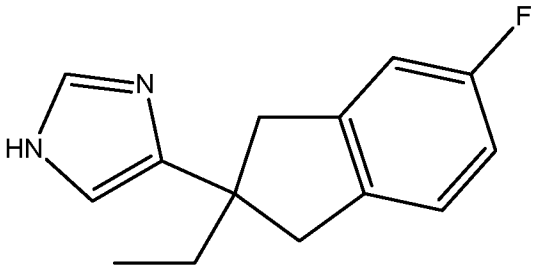


invention , wherein Y is CH_2 or CO, R_1 is a halogen or hydroxyl, R_2 is hydrogen or halogen and R_3 is hydrogen or lower alkyl-methyl (see abstract in a pharmaceutical composition administered orally (see abstract and also see col. 4, lines 62-63). Reasonably to have an oromucosal administration.

With regards to claim 25 Karjalainen teaches (see abstract



also) 4-(2-ethyl-5-fluoro-2,3-dihydro 1H indan-2-yl)-1H-imidazole is the same as



4-(2-ethyl-5-fluoro- indan-2-yl)-1H-imidazole or its acid salts (i.e., hydrochloride salt of (see col. 7, lines 48-50).

Karjalainen et al. also teach that the solvent is ethanol (as required by instant claim 27; see col. 7, lines 63-64).

However Karjalainen fails to teach specifically oromucosal administration and the addition of a preservative and a flavoring agent to the formulation (as required by

instant claims 26, 28, 29, 31-33). Even though Karjalainen failed to teach the addition of flavoring and or preservative it is however taught that "choosing auxiliary ingredients for the formulation is routine to the ordinary skill in the art and is evident that suitable solvents, colors etc are used in a normal way".

That being said it would have been obvious to one of ordinary skill in the art to add flavoring (i.e., sweetener) to the spray formulation for the improvement of the taste since the patient would preferably and willingly administer the sweet tasting spray versus a bitter tasting spay that is directly placed in the oromucosal cavity.
It would have been obvious to add a preservative to any drug formulation for the prolongation of shelf life. These are routine procedures employed in the art of formulation as indicated above by Karjalainen. It would have been obvious to one of ordinary skill in the art would have substituted Huupponen's compound with Karjalainen's since both compounds are α_2 adrenergic receptor antagonists and one would have reasonably expected the formulation for oromucosal to be successful.

7. Claims 23, 25-30 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huupponen (1995) and Karjalainen et al., (US 5,498,623) in view of De Prost (US 6,413,988) for the reasons made of record in Paper No. 20090911 and as follows.

Applicant argues that De Proost is not directed to α2- adrenergic receptor antagonists, and does not disclose any information concerning oromucosal vs. oral administration of fipamezole. Accordingly, the additional disclosure of this secondary

reference does not detract from the unexpected and surprising result achieved by the claimed method of administration.

In response it should be noted that De-Proost is added to show that preservatives and flavors addition to oral drug formulation are well known in the art.

In summary:

Huupponen and Karjalainen are applied here as above. However both Huupponen and Karjalainen fail to teach the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29, 30 and 33).

De Prost teaches an aqueous pharmaceutical solution of prucalopride employed as a spray for oral administration that comprises a preservative for inhibiting the growth of micro-organism (see col. 2, lines 30-45 and col. 3, lines 14-16) wherein the preservative is a parahydroxybenzoate salt (see col. 4, lines 58-67) and the flavor is aspartame and black currant (see col. 2, lines 46-47 and col. 3, lines 1-4).

However De Prost fails to teach the claimed compound femiprazole and oromucosal administration.

It would have been obvious to one of ordinary skill in the art to have employed the teaching of De Prost of a spray formulation with a preservative and a sweetener with the teaching set forth by Huupponen and Karjalainen because as taught by De Prost these are added to liquid oral formulations such as sprays to inhibit microbial growth and to affect the taste by masking the bitter tasting effect. As known to one of ordinary skill in the art, aspartame is an intense sweetener and therefore capable of masking

taste and black currant would give a fruity taste to the formulation and may enhance the sweetening capability of aspartame when combined.

Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Response to Affidavit

8. The declaration submitted by Jurg P. Seller under 37 CFR 1.132 filed 12/30/09 is insufficient to overcome the rejection of claims 23, 25-30 and 31-33 based upon the rejection set forth by Huupponen (1995) and Karjalainen et al. (US 5,498,623) or Huupponen (1995) and Karjalainen et al. in view of De Prost (US 6,413,988) as set forth in the last Office action because: the declaration contains specific dosage amounts not recited in the claims. Ex parte Gelles 22 USPQ 2d 1318 (at 1319): "The evidence relied upon also should be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter."

Also in order to claim unexpected result Applicant should note that there are three major points that should be considered:

The unexpected result must truly be unexpected, It must be commensurate in scope (show a trend representing the scope) and lastly a direct comparison with the closest prior art of record.

9. No claim is allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./
Examiner, Art Unit 1618,
02/18/10

/Robert C. Hayes/
Primary Examiner, Art Unit 1649